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Report No. 12-36

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Background: Recent research has suggested a relationship between vitamin D deficiency and risk of leukemia.

Purpose: Using data from the UN cancer database, GLOBOCAN, this study will determine whether a relationship exists for latitude and ultraviolet B (UVB) irradiance with incidence rates of leukemia in 175 countries.

Methods: Multiple regression was used to analyze the independent association between UVB and age-adjusted incidence rates of leukemia in 139 countries in 2002. This study controlled for dietary data on intake of energy from animal sources and per capita healthcare expenditures. The analyses were performed in 2009.

Results: People residing in the highest-latitude countries had the highest rates of leukemia in both men (R^2=0.34, p<0.0001) and women (R^2=0.24, p<0.0001). In men, UVB was independently inversely associated with leukemia incidence rates (p≤0.001), whereas animal energy consumption (p=0.02) and per capita healthcare expenditures (p≤0.0001) were independently positively associated (R^2 for model=0.61, p≤0.0001). In women, UVB adjusted for cloud cover was independently inversely associated with leukemia incidence rates (p≤0.01), whereas animal energy consumption (p≤0.05) and per capita healthcare expenditures (p=0.0002) were independently positively associated (R^2 for model=0.51, p<0.0001).

Conclusions: Countries with low UVB had higher age-adjusted incidence rates of leukemia. This suggests the possibility that low serum 25-hydroxyvitamin D status, because of lower levels of UVB, somehow might predict the development of leukemia.

(Am J Prev Med 2011;41(1):68–74) © 2011 Published by Elsevier Inc. on behalf of American Journal of Preventive Medicine.

Introduction

Approximately 300,500 new cases and 225,500 deaths from leukemia occur annually worldwide.[1] In the U.S., there are 43,050 new cases of leukemia and 21,840 deaths from leukemia each year.[2] Risk factors identified by previous research include exposure to tobacco smoke,[3] electromagnetic fields,[4] benzene,[5] and ionizing radiation.[6] However, the cause of most cases is unexplained.

The present study was intended to determine whether age-standardized incidence rates of leukemia are higher in high-latitude countries and to assess the relationship to ultraviolet B (UVB) with age-adjusted incidence rates while controlling for animal consumption and annual per capita healthcare expenditures. Many cancers have substantially higher incidence rates in areas of low solar UVB, including breast,[7,8] colon,[9–11] ovarian,[12,13] and renal.[13,14] This suggests that low serum 25-hydroxyvitamin D status, resulting from lower levels of UVB, somehow might predict the development of leukemia.

Greater exposure to solar UVB increases photosynthesis of vitamin D in the skin, resulting in higher levels of vitamin D metabolites, especially 25-hydroxyvitamin D, the predominant circulating form.[15] High concentrations of serum 25(OH)D may prevent leukemia through two key mechanisms. First, 25(OH)D plays a major role in the

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0749-3797/$17.00
doi: 10.1016/j.amepre.2011.04.003

up-regulation of e-cadherin,[16] a glue-like substance that keeps cells bound tightly together in a well-differentiated state. Second, high serum levels of 25(OH)D leave a greater amount of this metabolite to serve as substrate for synthesis of $1,25(OH)_2D$, which is synthesized in a wide range of tissues.[17] It also happens to be the most biologically active form of vitamin D.[18] Numerous laboratory studies have demonstrated the ability of $1,25(OH)_2D$ to promote differentiation of leukemic cells derived from humans[19–26] and animals.[27,28] They have also been shown to increase length of survival in animal models of leukemia.[29]

Previous research has implicated the consumption of red meats and other energy from animal sources with raising serum insulin-like growth factor (IGF-I) concentration,[30] which in turn has been hypothesized to be associated with higher incidence of childhood leukemia.[31] Further, because of differences in the amount of money governments spend per capita on health care, the ability to detect and accurately diagnose leukemia varies considerably by country. Therefore, the current study describes differences in incidence rates of leukemia according to latitude and UVB adjusted for cloud cover, while controlling for animal consumption and annual per capita healthcare expenditures.

Methods

Data Sources

Using data from the International Agency for Research on Cancer (IARC), GLOBOCAN, age-adjusted incidence rates of leukemia were obtained for 175 countries.[1] GLOBOCAN uses national cancer registries and vital statistics registers to estimate annual age-adjusted cancer incidence rates per 100,000 populations in 175 countries. The most recent year for which complete data were available was 2002.[1]

For each country, information was obtained on solar UVB at the top of the atmosphere at the winter solstice and total cloud cover as a percentage of sky covered. Population centroids, provided by the Center for International Earth Sciences Network of Columbia University, were used to determine the latitude for each country.[32] Total cloud cover was obtained from NASA satellite instrument packages and was measured as the mean proportion of the sky covered by clouds during the month of the winter solstice (December in the Northern hemisphere and June in the Southern).[33] Food data were available for 139 countries. Intake of animal protein as daily energy in kilocalories in 1980 was obtained from the UN Food and Agriculture Organization.[34] Year 1980 was used in order to allow the possibly 20-year latency period for leukemia to elapse.[35] Data on per capita health expenditures in international dollars in 2001 for each country were obtained from the WHO.[36]

In the Northern hemisphere, the spring equinox is around March 21–22 and in the Southern hemisphere it is around September 22–23. Total extraterrestrial solar UVB on the spring equinox, when the center of the sun is vertically overhead, was calculated using a standard formula.[37] The total extraterrestrial noon solar UVB on the spring equinox was calculated for each country using the formula ($A' = A \times \cos x$), where x is equal to latitude of the country in degrees, A is equal to total solar radiation at the equator in Watts/m^2, and A' is equal to total solar radiation for the country on the date of the vernal equinox in Watts/m^2.[37] Because UVB at ground level is approximately 1.4% of total extraterrestrial solar UVB, on the vernal equinox, it was multiplied by 0.014 in order to obtain the estimated UVB. Approximate ground-level UVB at solar noon on the equinox in each country was confirmed using data from Lubin et al.[38] The average fraction of the sky that was covered by clouds at the winter solstice was the measure of cloud cover, according to a NASA cloud measurement satellite that measures cloud cover from space.[33] The influence of fraction of cloud cover on transmission of UVB was adjusted for by multiplying extraterrestrial solar UVB by the mean fraction of sky not covered by clouds in winter for each country, using the following formula: UVB$\times$(1 − mean fraction of sky covered by clouds).

Statistical Analysis

Age-adjusted incidence rates for each country were plotted by latitude, and the best fit to the data points was obtained using a polynomial trend line. Multiple linear regression was used to assess the relationship between age-adjusted incidence rates of leukemia and extraterrestrial solar UVB in Watts/m^2 adjusted for cloud cover, while controlling for animal consumption, and per capita healthcare expenditure. UVB was estimated for the winter solstice (December 21 in the northern hemisphere and June 21 in the southern). Mean cloud cover was measured for the winter solstice in each hemisphere. Regression analyses were performed using JMP, version 5.1.2.

Results

Countries at the highest latitudes had highest age-standardized leukemia incidence rates in men ($R^2=0.34$, $p<0.0001$) (Figure 1) and women ($R^2=0.24$, $p<0.0001$) (Figure 2). (See Appendix A, available online at www.ajpmonline.org.) In the multivariate analysis, in men, after controlling for covariates, a 1 Watt/m^2 increase in solar UVB resulted in a decrease of 0.22 new cases of leukemia per 100,000 population per year ($p\leq0.001$), while animal energy consumption ($p=0.02$) and per capita health expenditure ($p\leq0.0001$) were independently positively associated (Table 1). In women after controlling for covariates, a 1 Watt/m^2 increase in solar UVB resulted in a decrease of 0.12 new cases of leukemia per 100,000 per year ($p=0.01$), whereas animal energy consumption ($p\leq0.05$) and per capita health expenditure ($p=0.002$) also were independently positively associated (Table 2).

To provide context, the mean annual incidence of leukemia worldwide is 6 per 100,000 men and 4 per 100,000 women. Stated in other words, a difference in incidence of leukemia of magnitude that was observed in the present study (specifically, a decrease of 0.22 new cases per 100,000 population per year per 1 Watt/m^2 of UVB irradiance) would be associated with occurrence of one fewer new case of leukemia for every 5 Watt/m^2 of higher UVB irradiance in

men, and one fewer new case of leukemia for every 8 Watt/m^2 of higher UVB irradiance in women. One fewer new case would amount to a one in six, or 16%, decrease in incidence in men and a one in four, or 25% decrease in incidence in women. The mean modeled extraterrestrial worldwide noon UVB irradiance adjusted for cloud cover was 8 Watts/m^2 (some further attenuation of UVB would have been likely at ground level because of unmeasured atmospheric factors). In any event, an increment of 1 Watt/m^2 corresponds to a 12% change from the mean worldwide cloud-adjusted noon extraterrestrial UVB of 8 Watt/m^2.

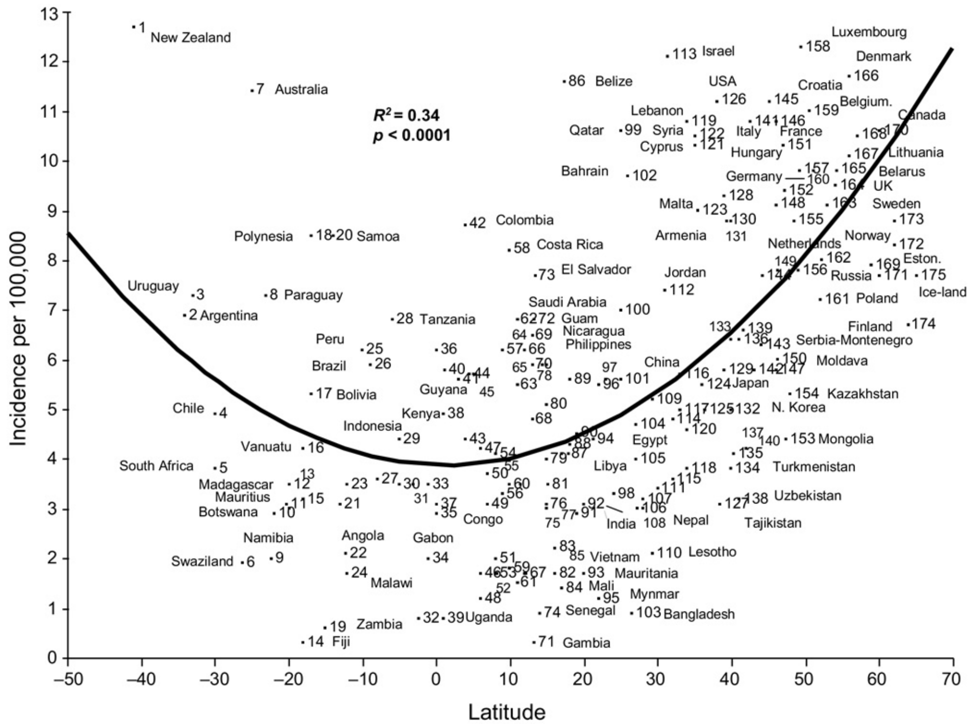

Figure 1. Incidence rates of leukemia per 100,000 population per year, men, 2002
Note: Source: Data from International Agency for Reserach in Cancer GLOBOCAN database.[1]
Points are labeled with country name where space allows. Countries with numerical labels only are listed in Appendix A (available online at www.ajpmonline.org).

Discussion

The results of the current study support literature suggesting that vitamin D (based on UVB) is protective against leukemia. However, some caution is appropriate in making such an interpretation. A possible alternative explanation could be that higher per capita income in countries distant from the equator, rather than lower UVB in those countries, could account for the higher incidence rates of leukemi+a observed in countries more distant from the equator. This concept seems to be supported by the existence of similar trends according to intake of animal energy and spending on health care, both of which are related to national per capita gross income. On the other hand, when intake of animal energy and per capita healthcare expenditures were included as covariates in a regression model, there was still an independent, substantial, and significant inverse association of UVB with incidence rates.

This is reassuring, as one reason for using these covariates in the regression model was to ensure that the association with UVB was not due to a more general effect of higher healthcare expenditures, or a diet high in animal energy, that could be characteristic of countries distant from the equator.

To more specifically examine the effect of per capita income, the authors performed a sensitivity analysis, repeating the regression model using per capita gross national income (GNI) instead of per capita health expenditures. The GNI was obtained from a UN statistical analysis of income.[39] The results using this regression model were virtually the same as the model using per capita healthcare expenditures and are therefore not reported separately.

The results of the present study are also consistent with results reported by Giovannucci and colleagues[40] from the Harvard Health Professionals Follow-Up Study. These investigators identified a relative risk of 0.5 for leukemia for each upward increment of 10 ng/mL in plasma 25-hydroxyvitamin D concentration ($p<0.05$). This important study is the first epidemiologic study of individuals, to our knowledge, that identified a risk reduction in leukemia incidence in association with higher serum 25(OH)D concentration.

The study by Giovannucci et al.[40] compared incidence rates of leukemia according to modeled 25(OH)D concentrations in individual men. The modeling algorithm used a regression approach that took into account the region of residence, race, physical activity, BMI, and the dietary and supplementary vitamin D intake of each participant. The subjects in that cohort study resided within the U.S., where differences in per capita income and healthcare expenditures are

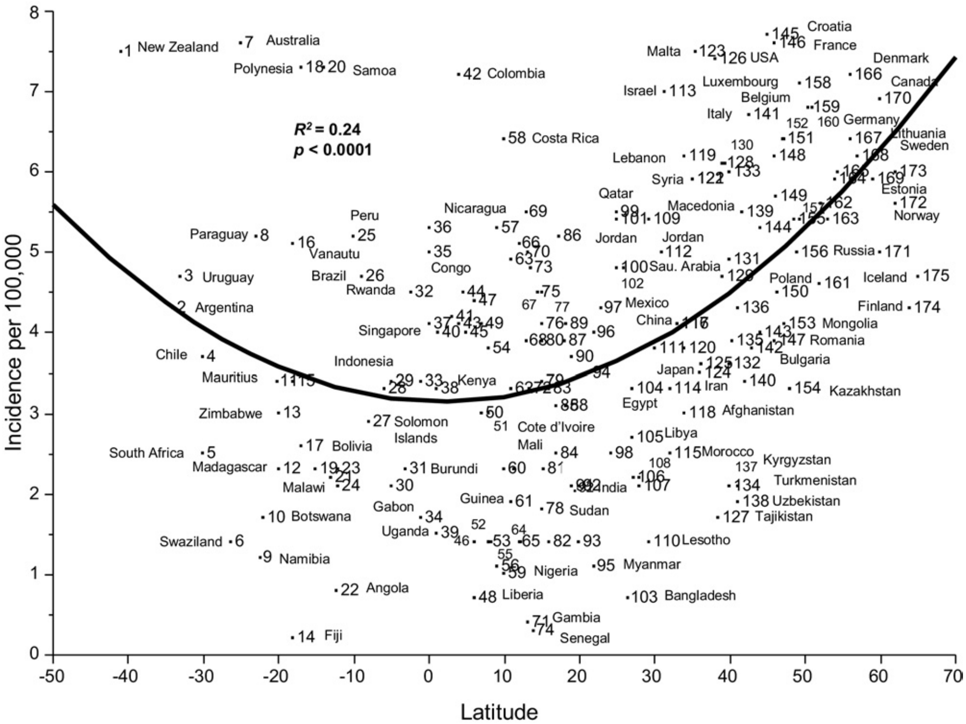

Figure 2. Incidence rates of leukemia per 100,000 population per year, women, 2002
Note: Source: Data from International Agency for Research in Cancer GLOBOCAN database.[1]
Points are labeled with country name where space allows. Countries with numerical labels only are listed in Appendix A (available online at www.ajpmonline.org).

relatively minor, compared to the differences that exist between the countries included in the current study. Therefore the results of the study by Giovannucci et al. support a substantial and significant inverse association between serum 25(OH)D concentration and incidence of leukemia that was unlikely to have been attributable to differences in income. This provides reassurance that the results of the present study are probably not due solely to differences in per capita income or health-care expenditures among countries.

There is also a considerable body of laboratory evidence that supports the involvement of vitamin D metabolites in suppressing the proliferation of human[19–26] and animal[28] leukemia cells in tissue culture systems. The most active vitamin D metabolite, 1,25(OH)$_2$D, increased the duration of survival in mice inoculated with human myeloid leukemia cells.[29] Despite notable advances in laboratory studies of the possible role of vitamin D in leukemia, only limited epidemiologic progress has been made to date in determining whether vitamin D deficiency might play some contributory etiologic role, beyond the known harmful effects of ionizing radiation,[6] benzene,[5] and tobacco smoke.[3]

The geographic pattern consisting of higher mortality rates of colorectal, breast, and ovarian cancer in the northeastern compared to the south and southwestern quadrants of the U.S. is less evident for leukemia. However, there is an inverse correlation between UVB levels and mortality from leukemia of lymphatic origin in Japan.[41] In addition, a study performed in northern Finland by Timonen[42] revealed that incidence rates of leukemia were higher in the cold, dark months than in the sunny months.

Contributions from environmental, occupational, and other risk factors are suspected, but only a few linkages have been made. The findings from this ecologic study

Table 1. Solar ultraviolet B irradiance and other covariates in association with leukemia incidence rates, 138 countries, men, 2002[a]

Variable	Regression coefficient	SE	R^2	*t*	*p*-value
Solar ultraviolet B irradiance (Watts/m^2)[b]	−0.2228	0.0660	0.49	−3.37	≤0.001
Intake of energy from animal sources (kcal)[c]	0.0019	0.0008	0.59	2.44	0.02
Per capita health expenditure (U.S. dollars)[d]	0.0012	0.0003	0.61	4.01	0.0001
Intercept	5.7884	0.8851		6.54	≤0.0001

Note: R^2=0.61, p<0.0001
[a]Source: International Agency for Research in Cancer GLOBOCAN database[1]
[b]Watts/m^2 at vernal equinox, adjusted for mean percentage cloud cover. Source: NASA International Satellite Cloud Climatology Project (ISCCP) satellite[33]
[c]Source: UN Food and Agriculture Organization[34]
[d]Source: WHO. All currencies were adjusted by WHO to U.S. dollars.[36]

suggest that vitamin D metabolites may exert some beneficial role in the etiology of leukemia, probably in conjunction with other factors. The other relevant factors are unknown. They might include an adverse association with per capita intake or animal consumption, which may contribute to the etiology of leukemia independently of low UVB. Intake of red meats and other energy from animal sources might theoretically account for this association, possibly because such intakes may be associated with higher serum IGF-1 concentrations.[30] High levels of IGF-1 have been hypothesized to be associated with higher incidence of childhood leukemia,[31] although more research is needed to test the hypothesis and determine whether it applies at older ages.

Table 2. Solar ultraviolet B irradiance and other covariates in association with leukemia incidence rates, 138 countries, women, 2002[a]

Variable	Regression coefficient	SE	R^2	t	p-value
Solar ultraviolet B irradiance (Watts/m^2)[b]	−0.1166	0.0459	0.39	−2.54	−0.01
Intake of energy from animal sources (kcal)[c]	0.0011	0.0005	0.46	1.94	≤0.05
Per capita health care expenditure (U.S. dollars)[d]	0.0007	0.0002	0.51	3.18	0.002
Intercept	4.1192	0.6157		6.69	<0.0001

Note: R^2=0.51, p<0.0001

[a]Source of incidence rates: International Agency for Research in Cancer GLOBOCAN database[1]

[b]Watts/m^2 at vernal equinox, adjusted for mean percentage cloud cover. Source: NASA International Satellite Cloud Climatology Project (ISCCP) satellite[33]

[c]Source: UN Food and Agriculture Organization[34]

[d]Source: WHO. All currencies were adjusted by WHO to U.S. dollars.[36]

Strengths

The present study had several strengths. To our knowledge, no previous study has analyzed age-standardized incidence rates of leukemia by latitude and UVB in such a large number of countries located at widely different latitudes. The multiple linear regression model that was developed in the current study accounted for 61% of the variance in leukemia rates in men and 51% in women. These models account for a substantial proportion of the worldwide variance in incidence rates. The independent contribution of UVB adjusted for cloud cover to leukemia incidence also was assessed while controlling for possible confounders such as per capita intake of energy from animal sources and per capita healthcare expenditures. These results were consistent with previous studies of the relationship between latitude or UVB and other cancers such as those of the colon,[43] breast,[44] and ovary.[45]

Intake of calories from animal sources had a strong positive correlation with incidence rates in both genders in the present study, consistent with previous studies that found an association between consumption of meat and incidence of childhood leukemia.[46,47] A covariate for per capita healthcare expenditure was included in the model in order to account for differences in the ability to detect cancers, which may be correlated with latitude because countries at higher latitude tend to be wealthier than countries at lower latitudes. However, UVB was still substantially and independently inversely associated with leukemia risk despite inclusion of this variable.

Limitations

The GLOBOCAN multi-country database enabled analysis of the relationship between ultraviolet radiation and cancer rates on a global scale, and demonstrated its value for hypothesis-generating studies. However, this is a study of aggregates (countries) rather than individual subjects. Findings that apply to aggregates may not apply to individuals. For example, all individuals living in areas of high UVB may not have high exposure to UVB. This could result from variations in clothing worn, urbanization, industrialization, and adoption of an indoor lifestyle. On the other hand, regional solar UVB tends to affect a broad range of individuals, and the finding was detected despite possible misclassification of exposure. Nondifferential misclassification of exposure generally obscures associations, rather than creating them.[48] Also, intake of energy from animal sources is a marker of industrialization and therefore might be related only indirectly to incidence rates.

A major limitation of the present study is the lack of distinction between types of leukemia. The most common types of leukemia in adults are acute myelogenous leukemia and chronic lymphocytic leukemia, whereas the most common form in children is acute lymphocytic leukemia. These types of leukemia are different from each other and should not be grouped together in the same category whenever possible. However, in the only source from which global incidence rates of leukemia are publicly available, the IARC GLOBOCAN database, no distinction is made between the different types of leukemia. All diagnoses falling under ICD 10 codes C91–C95 are grouped into the same category. Therefore, it is not possible to specify which subtype of leukemia that UVB and vitamin D may prevent.

Studies of this type should be considered as hypothesis-generating, rather than definitive. They are potentially the source of variables to be investigated with other methods. On the other hand, the diverse geographic distribution of populations in areas with different levels of UVB provides a natural experiment on a large scale. Natural experiments have been of value historically in identifying relevant risk factors for disease.[49]

Ecologic studies cannot account for all possible confounders. For example, the current study did not control for differences in physical activity among the populations of different countries. Still, there is no evidence supporting an association of low physical activity with leukemia, and effects of these or other factors are not mutually exclusive of favorable effects of UVB and vitamin D status.

The evidence from the present study suggests that UVB and, indirectly, vitamin D status, are inversely associated with the risk of leukemia. Studies of pre-diagnostic serum 25-hydroxyvitamin D levels in individuals, especially members of large cohorts, are needed to confirm this association. Additional epidemiologic studies are needed to determine if there is an inverse association of pre-diagnostic serum 25(OH)D concentrations with risk of leukemia in individuals.

Pending such studies, the present study provides some information relevant to ordinary life. Low exposure to solar UVB may contribute, in a limited way, to higher risk of leukemia in some countries. It may work alongside other etiologic factors, such as high intake of energy from foods of animal origin and environmental agents that have not been systematically measured in all countries. The importance of factors other than UVB and vitamin D is evident from the considerable heterogeneity in incidence rates that was present at most latitudes.

The beneficial association of solar UVB with leukemia incidence rates could be a result of vitamin D deficiency due to low solar UVB energy during the winter months in countries situated relatively distant from the equator as compared to closer to it. This tentative conclusion is consistent with a range of laboratory studies that have shown inhibition of leukemia cells by vitamin D metabolites in tissue culture, but it has not yet been proven.[50,51] Vitamin D deficiency may be one of several factors that contribute to risk of leukemia, but other factors are at least equally influential, and overall are more influential. These other factors are definitely deserving of further investigation in the pursuit of the multiple causes of leukemia.

This research was supported by a Congressional allocation to the Penn State Cancer Institute of the Hershey Medical Center, Hershey PA, through the Department of the Navy, Bureau of Medicine and Surgery, under Work Unit No. 60126 at the Naval Health Research Center (San Diego CA). The views expressed in this report are those of the authors and do not represent an official position of the Department of the Navy, Department of Defense, or the U.S. Government.

Thanks also to M. Ferlay and the staff of the International Agency for Research on Cancer, Lyon, France, for proving access to the GLOBOCAN database.

No financial disclosures were reported by the authors of this paper.

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Appendix

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.amepre.2011.04.003.

REPORT DOCUMENTATION PAGE

1. REPORT DATE (DD MM YY)
07 2012

2. REPORT TYPE
Journal submission

3. DATES COVERED (from – to)
2002-2008

4. TITLE
(U) Ultraviolet B and Incidence Rates of Leukemia Worldwide

5a. Contract Number:
5b. Grant Number:
5c. Program Element Number:
5d. Project Number:
5e. Task Number:
5f. Work Unit Number: 60126

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12-36

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10. SPONSOR/MONITOR'S ACRONYM(S)
NMRC/BUMED

11. SPONSOR/MONITOR'S REPORT NUMBER(s)

12. DISTRIBUTION/AVAILABILITY STATEMENT

Approved for public Release, distribution unlimited.

13. SUPPLEMENTARY NOTES
American Journal of Preventive Medicine, 2011, 41(1), 68–74

14. ABSTRACT
Background: Recent research has suggested a relationship between vitamin D deficiency and risk of leukemia.

Purpose: Using data from the UN cancer database, GLOBOCAN, this study will determine whether a relationship exists for latitude and ultraviolet B (UVB) irradiance with incidence rates of leukemia in 175 countries.

Methods: Multiple regression was used to analyze the independent association between UVB and age-adjusted incidence rates of leukemia in 139 countries in 2002. This study controlled for dietary data on intake of energy from animal sources and per capita healthcare expenditures. The analyses were performed in 2009.

Results: People residing in the highest-latitude countries had the highest rates of leukemia in both men (R^2=0.34, $p<0.0001$) and women (R^2=0.24, $p<0.0001$). In men, UVB was independently inversely associated with leukemia incidence rates ($p<0.001$), whereas animal energy consumption ($p=0.02$) and per capita healthcare expenditures ($p<0.0001$) were independently positively associated (R^2 for model=0.61, $p<0.0001$). In women, UVB adjusted for cloud cover was independently inversely associated with leukemia incidence rates ($p<0.01$), whereas animal energy consumption ($p<0.05$) and per capita healthcare expenditures ($p=0.0002$) were independently positively associ- ated (R^2 for model=0.51, $p<0.0001$).

Conclusions: Countries with low UVB had higher age-adjusted incidence rates of leukemia. This suggests the possibility that low serum 25-hydroxyvitamin D status, because of lower levels of UVB, somehow might predict the development of leukemia.

15. SUBJECT TERMS
vitamin D, leukemia, ultraviolet rays, incidence, international comparison

16. SECURITY CLASSIFICATION OF: a. REPORT	b. ABSTRACT	c. THIS PAGE	17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	18a. NAME OF RESPONSIBLE PERSON
UNCL	UNCL	UNCL	UNCL	8	Commanding Officer

18b. TELEPHONE NUMBER (INCLUDING AREA CODE)
COMM/DSN: (619) 553-8429